Acta Paediatrica Academiae Scientiarum Hungaricae, Vol. 19 (1), pp. 1–7 (1978)

Mucocutaneous lymph node syndrome: Three cases observed in Hungary

By

G. Nyerges, Mária Barna and L. Molnár

Hospital for Infectious Diseases, Budapest

Received 21st October, 1976

Three patients are reported whose symptoms were very similar to those described in mucocutaneous lymph node syndrome, a disease prevalent in Japan. In one case the disease was complicated by otomastoiditis which prolonged the course and reactivated the symptoms. In the other two cases recovery was uneventful. No epidemiological relation could be demonstrated among the cases. Prednisolone was administered to two patients with immediate antifebrile effect.

The mucocutaneous lymph node syndrome (MLNS) is a disease with fever and rash common in Japan. The disease was first reported by Kawasaki in 1967 [8] and a few years later Kawasaki et al. [9] published a detailed study of more than 6000 cases and summarized the clinical and epidemiological features. Since then some cases have been observed in the USA and Canada [2, 4, 7, 11, 12, 13, 14, 15] and in Europe [1, 16].

The main symptoms are: fever lasting 1 to 2 weeks not responding to antibiotics; conjunctivitis; dryness, reddening and fissuring of lips; reddening and prominence of tongue papillae ("strawberry tongue"); reddening of palms and soles with indurative oedema of hands and feet, followed by membranaceous desquamation from the fingertips; polymorphous exanthem on the trunk and non-suppurative cervical lymphadenitis. Other symptoms are arthralgia or arthritis, diarrhoea, albuminuria, pyuria, aseptic meningitis and mild jaundice. The most severe change is coronary thrombarteritis leading to aneurysms and thrombotic occlusion with myocardial infarction or ischaemia [1, 17].

The most consistent laboratory abnormalities found in MLNS are elevated ESR, leukocytosis with a shift to the left, slight anaemia, positive C-reactive protein, negative antistreptolysin-O titre, increased alpha$_2$-globulin level.

The aetiology of MLNS is unknown. Rickettsia-like bodies have been found in biopsy and autopsy specimens from patients with MLNS [3, 5, 6].

We present three cases from Hungary, the symptoms of which were very similar to those described for MLNS.

Case Reports

Case 1. S. P., a one-year-old girl, was admitted on February 17, 1976, with symptoms suggesting measles. Formerly, apart from a mild facial eczema, she had been healthy and developed well. She had been vaccinated with BCG, DPT and live polio vaccine types 1 and 3 without any inconvenience. Six days before admission she had developed fever up to 39°C and a rash. The rash was maculopapular; it was first seen on the trunk and by next day it had spread all over the body. The baby then developed coryza with sanguino-purulent discharge, her lips became swollen, dry and fissured. The doctor diagnosed measles and gave her penicillin and antipyretics. On the third day the exanthem faded but the fever persisted. On the 4th day the exanthem reappeared on the face and the eyelids, the hands and feet became swollen.

On admission the baby had a toxic appearance. Her eyelids were red and swollen, there was a maculopapular rash on the face. The lips were red, swollen and fissured. Some slightly swollen cervical lymph nodes were palpable. The hands and feet were also swollen with erythema on the palms and soles. A fusiform swelling of the fingers with a lilac-red coloured skin over the joints could be observed (Fig. 1). There was a dry eczema on the legs. Oral and pharyngeal mucosa were reddened, the papillae of the tongue were red and prominent.

Physical examination revealed no abnormality over the chest. The abdomen was moderately swollen, the liver was palpable 1 cm below the right costal margin. No neurological sign could be observed. Rectal temperature was 38.7°C, the chest X-ray was normal. ESR on admission was 8 mm/hr, WBC 5800 with 6% band forms, 36% polynuclears and 56% lymphocytes. Haemoglobin, 9.8 g/dl; haematocrit, 30%. The urine was negative. A throat swab culture revealed no pathogenic bacteria, the blood culture was sterile.

In view of the fever and the sanguino-purulent discharge from the nose, erythromycin therapy was started. The rash, swelling of hands, feet and digits were thought to be of allergic nature and though penicillin was suspected as allergen, penicillin skin tests gave negative results.

During the next two weeks the child had fever persisting between 38 and 39°C. At the end of the first week of hospitalization the ESR increased to 110 mm/hr, and the child developed leukocytosis and anaemia (WBC 17,200, with 21% immature and 58% mature polynuclears, 3% eosinophils, 13% lymphocytes and 5% monocytes; haemoglobin, 8.0 g/dl). The abdominal swelling increased and she had diarrhoea for a few days. Otherwise no pain or mass could be found in the abdomen and the abdominal X-rays were normal.

The fever, leukocytosis and increased ESR suggested a septicaemia of unknown origin and ampicillin, cephalosporin and gentamycin therapy was introduced. The symptoms persisted unchanged for another week and even a swelling of the left shoulder appeared. Repeated urine examinations, X-rays of chest and bones, examination of paranasal sinuses, ears, and pyelography revealed no septic focus and the repeated blood culture was also sterile. Other laboratory findings were, serum protein, 6.0 g/dl; albumin, 3.24 g/dl; alpha$_1$-globulin, 0.36 g/dl; alpha$_2$-globulin, 1.2 g/dl; beta-globulin, 0.84 g/dl; gamma-globulin, 0.36 g/dl; IgG, 579 mg/dl; IgM, 108 mg/dl; IgA, 40 mg/dl. Serum electrolytes, urea nitrogen, alkaline phosphatase, transaminases, aldolase, bilirubin were normal, the latex test was negative. LE phenomenon was also negative. Measles and rubella HAI-titre was repeatedly negative. Adenovirus C'BR: 1 : 4, later 1 : 128; antistreptolysin-O titre repeatedly 86 Todd units. C-reactive protein, 1 : 70, later 1 : 400. Repeated throat swabs, urine, stool and blood cultures were negative. The ECG showed no abnormality.

By the end of the second week of hospitalization the symptoms decreased, the general condition improved, and a membranaceous desquamation from the fingertips started. The ESR decreased to 70 mm/hr. In the third week the fever rose again, the mucous membrane, skin and joint symptoms reappeared. At that time otoscopy revealed a purulent otitis media and repeated ear X-rays pointed to mastoiditis. On the 23rd day of hospitalization, mastoidectomy was performed; it revealed a purulent process but no pathogenic bacteria could be isolated from the pus. In spite of the mastoidectomy the fever and the symptoms persisted for another week and the ESR increased again to 100 mm/hr. The fever ceased in the 5th week, and the other symptoms gradually disappeared by the end of the 7th week. By that time the baby's appetite improved, she gained weight, ESR and blood counts became normal. She was discharged after two months hospitalization.

When the child was seen two months later, she was asymptomatic and the laboratory findings were normal.

Case 2. R. M., a previously healthy 16-month-old girl, was admitted with the diagnosis of scarlet fever on January 14, 1977. She had developed fever and rash two days before admission and had been given penicillin.

On admission the child had a scarlatiniform exanthem and sore throat, therefore penicillin therapy was continued. The fever persisted and a maculopapular rash appeared on the arms and legs; the palms and soles were reddened. An allergy to penicillin was supposed and penicillin therapy was discontinued. During the following days the child became distressed. Dryness, reddening and fissuring of the lips, diffuse reddening of oral and pharyngeal mucosa, a "strawberry tongue", conjunctivitis, mild coryza and moderate enlargement of the cervical lymph nodes developed. She had loose stools. No other organic changes could be demonstrated by physical, X-ray or ECG examination.

Laboratory findings were, ESR, 88 mm/hr; RBC, 3,400,000; haemoglobin, 9.2 g/dl; WBC, 10,200, with 8% band forms, 68% polynuclears, 22% lymphocytes and 2% monocytes. Antistreptolysin-O, 143 Todd units; C-reactive protein, 1 : 1120; serum protein, 6.8 g/dl; albumin, 3.2 g/dl; alpha$_1$-globulin, 0.4 g/dl; alpha$_2$-globulin, 1.08 g/dl; beta-globulin, 0.68 g/dl; gamma-globulin, 1.42 g/dl. Serum electrolytes, urea nitrogen, bilirubin, alkaline phosphatase, transaminases, aldolase were normal. A mild proteinuria and leukocytes in the urinary sediment were found. No pathogenic bacteria were isolated from the throat, stools and urine. Blood culture was negative. Attempts to isolate respiratory or enteroviruses remained unsuccessful. No antibodies to measles, rubella and adenoviruses were found in repeated serum samples.

In spite of antibiotics (gentamycin, tetracycline, erythromycin) an intermittent fever persisted for 17 days while the rash and the mucous membrane signs gradually disappeared and a membranaceous desquamation from the fingertips was noticed. From the 15th day of hospitalization prednisolone therapy was introduced whereupon the child became afebrile within two days. ESR and blood counts became normal within ten days. After six weeks of hospitalization the child was discharged symptom-free. A month later she was healthy and well.

Case 3. K. T., a previously healthy 6-year-old girl, was admitted with the diagnosis of scarlet fever on May 16, 1977. She had a four-day history of fever, sore throat, bilateral painful enlargement of cervical lymph nodes, conjunctivitis and polymorphous exanthems all over the body. She had been treated with penicillin.

On admission she had fever, but her general condition was good. On the arms and legs a polymorphous while on the trunk a scarlatiniform exanthem was seen. The bulbar conjunctivae were congested; the lips were swollen, dry, red and fissured (Fig. 2). The oropharyngeal mucosa was

also congested with some small ulcerations. The tongue papillae were red and swollen. A few moderately enlarged cervical lymph nodes were palpable. Oedema of hands and feet with diffuse erythema of the palms and soles was observed.

An innocent systolic murmur was heard in the II—III costal space along the left sternal border. No abnormality was found over the lungs by physical examination. The liver and the spleen were palpable 1 cm below the costal margins. X-rays of chest and ECG showed normal conditions.

Laboratory findings were, ESR, 120 mm/hr; RBC, 3,500,000; haemoglobin, 10.8 g/dl; WBC, 10,000 with 14% band forms, 60% polynuclears, 22% lymphocytes, 2% monocytes and 2% eosinophils. Antistreptolysin-O titre, 84 Todd units. On admission C-reactive protein, 1 : 200, one week later, 1 : 400. Serum protein, 6.3 g/dl; albumin, 3.4 g/dl; alpha$_1$-globulin, 0.44 g/dl; alpha$_2$-globulin, 1.02g/dl; beta-globulin, 0.38 g/dl; gamma-globulin, 1.02 g/dl; IgG, 1731 mg/dl; IgM, 216 mg/dl; IgA, 223 mg/dl. Urine was negative. Serum electrolytes, urea nitrogen, bilirubin, alkaline phosphatase, transaminases, aldolase were normal. No pathogenic bacteria were found in the throat-swab, stool and urine cultures. From repeated blood cultures *Streptococcus viridans* was isolated on one occasion. No respiratory or enteroviruses could be isolated. On admission the measles HAI titre was 1 : 80, rubella HAI titre 1 : 256; adenovirus C'BR, 1 : 16. These titres were unchanged when examined three weeks later.

After admission, penicillin therapy was continued, but the fever persisted. During the second week of hospitalization a mild diarrhoea developed. Since the clinical picture and the laboratory findings showed all the characteristics of MLNS, the patient was given prednisolone from the 6th to 12th days of hospitalization. On the second day of prednisolone therapy the child became afebrile and remained so until discharge. The mucocutaneous signs gradually disappeared and a membranaceous desquamation from the fingertips developed at the end of the second week (Fig. 3). The child was discharged symptom-free after one month of hospitalization.

Discussion

The MLNS has no definitive diagnostic criteria. The diagnosis is based on a special combination of symptoms which separately or in other combinations can be found in other diseases as well. The usual symptoms and their frequency given by Kawasaki et al. [9] are presented in Table I; it also shows which of the symptoms were present in our cases. In Case 1 only two of the principal symptoms were lacking. These two were conjunctivitis and polymorphous exanthems on the trunk, but both had been noticed by the doctor at home, who diagnosed the symptoms as measles. The rash in some MLNS cases has in fact been described as a morbilliform one [13]. The repeatedly negative measles HAI-tests, however, excluded the diagnosis of measles. In Case 2 only the indurative oedema of hands and feet was lacking, while in Case 3 all the principal symptoms were present.

In addition to the principal symptoms arthritis was present in one, leukocyturia and proteinuria in one and diarrhoea in all the three cases.

All the characteristic laboratory abnormalities could be found in the cases presented, thus increased ESR, leukocytosis, slight anaemia, negative antistreptolysin-O titre,

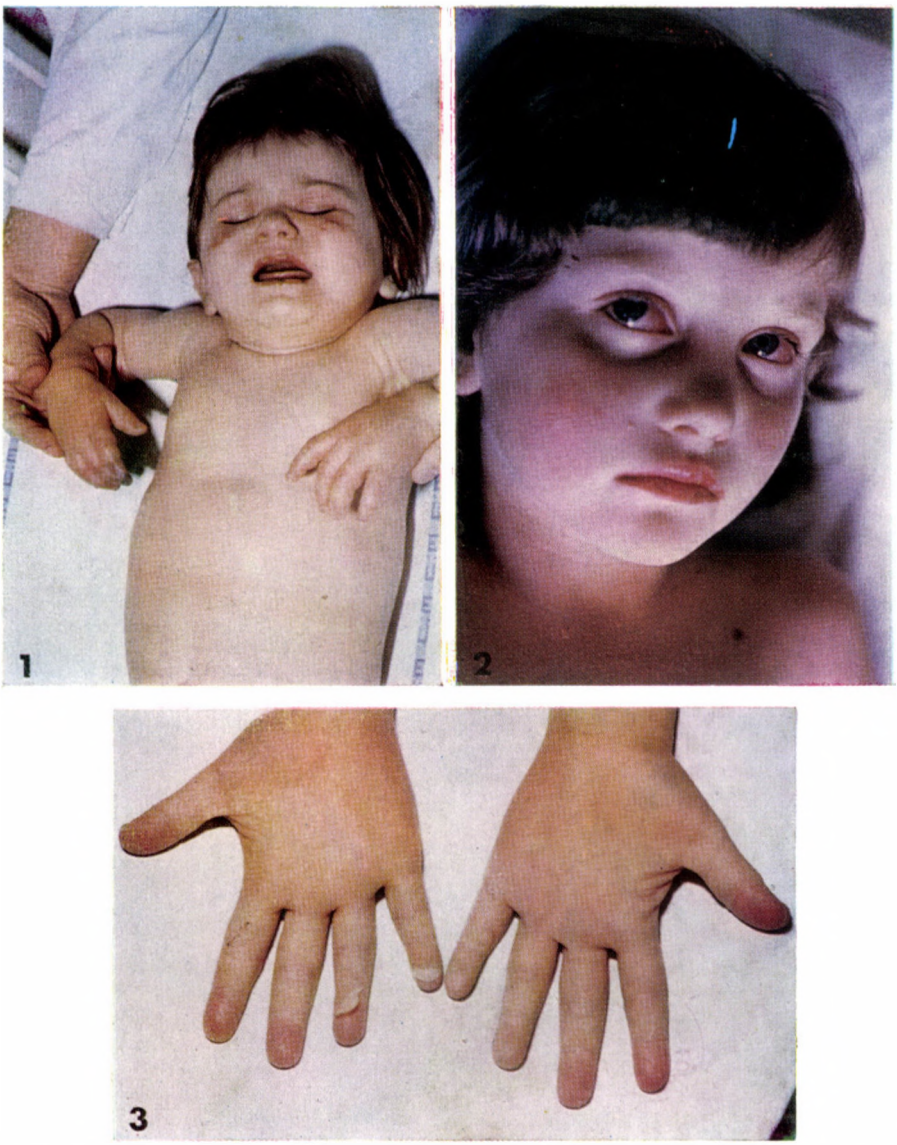

FIG. 1. Case 1. Red and swollen eyelids; maculopapular rash on face; swollen and fissured lips; oedema of hands; fusiform swelling of fingers with lilac-red coloured skin over the joints

FIG. 2. Case 3. Congested conjunctivae; diffuse erythema on face; swollen and fissured lips

FIG. 3. Case 3. Membranaceous desquamation from the fingertips

TABLE I

Symptoms of MLNS according to Kawasaki [9] and their presence in our cases

Symptoms	Frequency, per cent	Presence in case		
		1	2	3
Principal symptoms				
Fever lasting from one to two weeks and not responding to antibiotics	95	+	+	+
Bilateral congestion of ocular conjunctivae	88	±	+	+
Changes in lips and oral cavity				
Dryness, redness and fissuring of lips	90	+	+	+
Protuberance of tongue papillae	77	+	+	+
Diffuse reddening of oral and pharyngeal mucosa	90	+	+	+
Changes in peripheral extremities				
Reddening of palms and soles	88	+	+	+
Indurative oedema	76	+	−	+
Membranaceous desquamation from fingertips	94	+	+	+
Polymorphous exanthem on trunk without vesicles or crusts	92	±	+	+
Acute nonpurulent swelling of cervical lymph nodes 1.5 cm or more in diameter	75	+	+	+
Other significant symptoms or findings				
Carditis, especially myocarditis and pericarditis		−	−	−
Diarrhoea		+	+	+
Arthralgia or arthritis		+	−	−
Proteinuria and increase of leukocytes in urine sediment		−	+	−
Changes in blood tests				
Leukocytosis with shift to the left		+	+	+
Slight decrease in erythrocyte and haemoglobin levels		+	+	+
Increased ESR		+	+	+
Increased $alpha_2$-globulin		+	+	+
Positive CRP		+	+	+
Negative ASLO		+	+	+
Changes observed occasionally				
Aseptic meningitis		−	−	−
Mild jaundice or slight increase of serum transaminase		−	−	-

positive C-reactive protein, increased $alpha_2$-globulin level; though in Case 1 some of them (increased ESR, leukocytosis) developed only during the second week of the disease.

We believe that in our cases the combination of symptoms and signs closely resembled those described in MLNS. Other diseases with similar symptoms such as scarlet fever, sepsis, juvenile rheumatoid arthritis, Stevens—Johnson syndrome, periarteritis nodosa could be excluded on the basis of the absence of special symptoms and the differing clinical course [9, 13].

In Case 1, the course of the illness differed somewhat from that outlined

in the literature. In the cases reported from Japan the disease lasted 2 to 3 weeks, but our patient became symptom-free only by the end of the 7th week. The other difference in this case was the otomastoiditis which has not been mentioned among the symptoms of MLNS. The protracted course may have depended on the otomastoiditis that developed in the third week and in fact we observed that the symptoms which by the end of the second week had improved reappeared when the fever again became higher. The question arises whether the disease observed was a sepsis associated with an initially latent mastoiditis. Though many symptoms of MLNS occur in sepsis, the observed combination is not characteristic of sepsis. Looking at the course of the disease, otomastoiditis seemed rather a complication of MLNS.

Two of our aetiological tests gave a positive result. In Case 1 the adenovirus complement-binding titre increased from 1 : 4 to 1 : 128 during the disease. Though this points to an adenoviral infection, we do not believe in its aetiological role. On the one hand, there is no similar observation in the literature, and on the other, if an adenoviral infection had an aetiological role in MLNS, it is highly improbable that MLNS would be so rare considering the frequency of adenoviral infections. In all probability it was a concomitant infection in our Case. In case 3, *Streptococcus viridans* was isolated from one of the blood cultures. Since no similar symptoms caused by *Streptococcus viridans* had been reported, we believe that it was an accidental finding without any aetiological importance.

There had been no contact among our cases. Cases 1 and 2 originated from two villages far from each other and from Budapest. Case 3 came from Budapest. There was a one-year interval between admission of the first and the second case and a three-month interval between the second and the third case. No similar disease in the patients' families was reported.

As to the therapy, prednisolone was administered to two of our patients. In accordance with the literary data [9] it had an immediate antifebrile effect. Though the aetiology of MLNS is unknown, the beneficial effect of prednisolone and the observation that the serum IgE level increases during the disease [10] suggest that allergy may have an important role in the pathogenesis of MLNS.

References

1. Ahlström, H., Lundström, N.-R., Mortensson, W., Östberg, G., Lantorp, K.: Infantile periarteritis nodosa or mucocutaneous lymph node syndrome. Acta paediat. scand., **66,** 193 (1977).
2. Brown, J. S., Billmeier, G. J., Cox, F.: Mucocutaneous lymph node syndrome in the continental United States. J. Pediat. **88,** 81 (1976).
3. Carter, R. F., Haynes, M. E., Morton, J.: Rickettsia-like bodies and splenitis in Kawasaki disease. Lancet **2,** 1254 (1976).
4. Darby, C. P., Kyong, C. U.: Mucocutaneous lymph node syndrome. J. Amer. med. Ass. **236,** 2295 (1976).

5. Hamashima, Y., Kishi, K., Tasaka, K.: Discovery and isolation of rickettsia-like bodies from M. C. L. S. patients. Progr. Med. (Tokyo) **87,** 189 (1973).
6. Hamashima, Y., Kishi, K., Tasaka, K.: Rickettsia-like bodies in infantile acute febrile mucocutaneous lymph node syndrome. Lancet **2,** 42 (1973).
7. John, T. J., DeBenedetti, C. D., Zee, M. L.: Mucocutaneous lymph node syndrome in Arizona. Amer. J. Dis. Child. **130,** 613 (1976).
8. Kawasaki, T.: M. C. L. S. — Clinical observation of 50 cases. Jap. J. Allerg. **16,** 178 (1967).
9. Kawasaki, T., Kosaki, F., Okawa, S., Shigematsu, L., Yanagawa, H.: A new infantile acute febrile mucocutaneous lymph node syndrome (MLNS) prevailing in Japan. Pediatrics **54,** 271 (1974).
10. Kusakawa, S., Hainer, D. C.: Levels of immunoglobulin E in the acute febrile mucocutaneous lymph node syndrome. Pediat. Res. **10,** 108 (1976).
11. Kim, J., Yeo, Y., Lee, D. B.: Coronary aneurysms in infants and young children with acute febrile mucocutaneous lymph node syndrome. J. Pediat. **86,** 892 (1975).
12. Lauer, B. A., Bruhn, F. W., Todd, J. K., Todd, W. A.: Mucocutaneous lymph node syndrome in Denver. Amer. J. Dis. Child. **130,** 610 (1976).
13. Melish, M. E., Hicks, R. M., Larson, E. J.: Mucocutaneous lymph node syndrome in the United States. Amer. J. Dis. Child. **130,** 599 (1976).
14. Radford, D. J., Sondheimer, H. M., Williams, G. J., Fowler, R. S.: Mucocutaneous lymph node syndrome with coronary artery aneurysm. Amer. J. Dis. Child. **130,** 596 (1976).
15. Russel, A. S., Zaragoza, A. J., Shea, R.: Mucocutaneous lymph node syndrome in Canada. Canad. med. Ass. J. **112,** 1210 (1975).
16. Valaes, T.: Mucocutaneous lymph node syndrome (MLNS) in Athens, Greece. Pediatrics **55,** 295 (1975).
17. Yamagisawa, M., Kobayashi, N., Matsuya, Sh.: Myocardial infarction due to coronary thrombarteritis following acute febrile mucocutaneous lymph node syndrome (MLNS) in an infant. Pediatrics **54,** 277 (1974).

G. Nyerges, M. D.
Gyáli út 5–7
H–1097 Budapest, Hungary